REMARKS/ARGUMENT

Examiner Haghigatian and S.P.E. Richter are thanked for courtesies extended during a personal interview of this application conducted August 29, 2007. In accordance with M.P.E.P. §713.04, the substance of the interview is summarized in the next section hereof. The present amendment and enclosures are in accordance with the discussions at the interview. Among the enclosures herewith is a Second Declaration of Inventor William Stern under 37 CFR §1.132 (hereinafter "Stern-II"). Also included is a Supplemental Declaration for Reissue Patent Application to Correct "Errors" Statement (37 C.F.R. 1.175) signed by the inventor. Reconsideration of the application, and issuance of a notice of allowance, is requested in view of the amendments, enclosures and remarks herein.

SUMMARY OF INTERVIEW SUBSTANCE UNDER M.P.E.P. § 713.04

A personal interview was held at the U.S. Patent and Trademark Office on August 29, 2007. In attendance were Examiner Mina Haghigatian, Supervisory Patent Examiner Johann Richter, Inventor William Stern and Applicant's Representative, William Gray.

Claims 13-18, 20-21 and 24-44 were discussed in connection with the "new matter" rejection. Applicant confirmed a prior agreement that the word "such" would be removed from claims 13 and 15, and that the specification would be amended to add a range of osmotic pressure identical to the range recited in claim 15. Those two changes are now of record by virtue of the present amendment. Dr. Stern explained that, because of the Henderson-Hasselbach equation, Table 1 necessarily reports the results achieved by formulations that include a mixture of citric acid and ciric acid salt - - not merely citric acid alone. The Examiner indicated that, once Dr. Stern has confirmed his foregoing Henderson-Hasselbach analysis in a filed declaration under Rule 132, the "new matter" rejections will likely be withdrawn. Enclosed Stern-II, paragraphs 5-6 confirms this analysis.

Claims 13-14, 17, 20-21, 34, 38, 40-42 were discussed in connection with the anticipation rejection over Chiodini. It was pointed out that example 19 of Chiodini, specifically referenced by the Examiner, adjusted pH to 6 - - well outside of the range of applicant's claims 13-14, 17, 20-21, 34, and 40-42. It was agreed that the foregoing claims are not anticipated by Chiodini for the

foregoing reason, and further because the mere partial overlap of applicant's narrow claimed ranges relative to much broader ranges discussed elsewhere in the Chiodini text does not amount to an anticipation under the holding of *Atofina v. Great Lakes Chemical Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) discussed in more detail, *infra*. Claims 18 and 22-23 (not discussed in connection with Chiodini at the interview) have specific limitations not disclosed by Chiodini, which limitations are discussed in the section regarding Chiodini, *infra.*

Claims 13-14, 17, 20-23, 34 and 40-42 were discussed in connection with the anticipation rejection over Grebow. Applicant noted that all claims are limited to a narrow concentration range of citric acid and/or citric acid salt (10-25 mM in some claims; 10-50 mM in others) , whereas Grebow teaches a broad concentration range from 10-500mM. It was agreed that an overlap of that nature does not constitute an anticipation under the holding of *Atofina v. Great Lakes Chemical Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) as discussed in more detail in the Grebow section, *infra*.

Claims 15-16, 18-19, 24-33, 35-39 and 43-44 were discussed in connection with the obviousness rejection over the combination of Grebow and Azria. Applicant noted that the rejected claims are limited to a critical 10-25 mM or 10-50 mM concentration range of citric acid (and/or citric acid salt) that is not believed to be suggested by Grebow's broad range of 10-500 mM. It was further pointed out by applicant that Azria does not utilize citric acid or citric acid salt at all, and thus cannot add anything to the teachings of Grebow in this regard. Regarding Grebow, applicant argued both (1) that a prima facie case of obviousness was not made under *In re Fine,* 837 F.2d 1071, 1075-76 (Fed. Cir. 1988), cited for the proposition that *prima facie* obviousness requires that the overlapping ranges be for the same purpose in the prior art as in the claims; and (2) that even if a *prima facie* case had been made, applicant rebutted any *prima facie* case by showing unexpected results as permitted by *In re Peterson*, 315 F.3d 1325 (Fed. Cir. 2003). While not specifically discussed at the interview, Applicant also relies on *In re Soni*, 54 F.3d 746 (Fed. Cir. 1995) in connection with analyzing the obviousness rejection, *infra*.

At the interview, regarding whether *prima facie* obviousness had been established, Dr. Stern noted his belief that Grebow discussed citric acid for a different purpose - - adjusting pH - - not for applicant's purpose of improving bioavailability while maintaining shelf stability. Applicant noted that Grebow did not report testing for shelf stability, and that Grebow's testing for

bioavailabilty tested only the effect of aminolevulinic acid in formulations that did not have any citric acid or citric acid salt at all. Regarding unexpected results, applicant noted that Tables 1 and 3 show a critical range of citric acid (and/or citric acid salt) for simultaneously achieving adequate bioavailability and shelf stability. Dr. Stern pointed out, in particular, the unexpected loss of shelf stability as citric acid (and/or citric acid salt) increases in Table 3. He noted his belief that this is likely caused by the quite unexpected formation of an adduct between citric acid and calcitonin (although other mechanisms are also possible for Table 3's observed reduced shelf stability at high citrate concentration). Dr. Stern indicated that a third party report prepared for Unigene, the assignee of this application, is available and shows formation of the foregoing adduct. That report is attached as Exhibit A to the enclosed Stern-II Declaration (Stern-II, paragraph 12). The Examiner reserved judgment on whether the foregoing overcomes the obviousness rejection, pending her further review of the case law and of Dr. Stern's further Rule 132 Declaration (enclosed herewith). The relevant case law is analyzed in further detail in the obviousness section, *infra*.

Finally, applicant noted that there were some errors in the text of the specification, and in some of the numbers set forth in Tables 1 and 3 that would be corrected in the amendment. S.P.E. Richter indicated that these errors, if supported by laboratory notebooks or the like, could likely be corrected as inherent, without raising "new matter" issues. It was also noted that other data related to bioavailability or shelf stability of calcitonin formulations would be submitted. The present amendment and accompanying Stern-II Declaration address these issues.

SUMMARY OF THE PRESENT AMENDMENT

In accordance with Rule 173(g), all of the amendments herein are relative to the issued patent -- not relative to the text that existed prior to the present amendment. In the present amendment, the specification has been amended in the manner requested by the Examiner, and agreed to by applicant, during the interview. Specifically, a further reference to the range of 250 to 350 mOsm/liter has been added to the specification at column 3, lines 15-20. Also, the word "such" has been removed from claims 13 and 15.

Additionally, the citric acid and/or citric acid salt in claim 24 is now recited as 20 mM to avoid redundancy over claim 15, and various specification errors are corrected. The specification corrections are explained in more detail at Stern-II, paragraphs 15-21, and exhibits thereto. It was indicated at the recent interview that amendments to the specification that were supported by laboratory notebooks could be made without raising new matter issues. The above Stern-II citations are believed to provide appropriate documentation. Additionally, the changes made in columns 1-4 of the specification are obvious typographical, spelling or grammatical errors. The changes to the Example 1 and Example 2 preambles (prior to Tables 1 and 2) are supported by the description of procedure at column 4, lines 38-43 of the specification. The concentration unit "mM" in Table 1 was in applicant's provisional application 60/180,241 and nonprovisional application 09/776,537. Its failure to appear in printed Patent No. 6,440,392 is believed to be an office printing error, and is corrected herein. The remaining changes are believed to be covered by Stern-II and exhibits thereto.

35 U.S.C. § 112 REJECTION (WRITTEN DESCRIPTION/ NEW MATTER)

In the most recent office action, the Examiner had alleged that the range of "10-25 mM" for the bioavailability enhancing agent, as stated in claims 13-18, 20, 21 and 24-44 is not supported by the specification as originally filed. During last year's interview (held October 5, 2006), the Examiner had noted that Table 1, in column 5 of the original patent, appeared to support the 10-25 mM range, but only for citric acid and not necessarily for the combination of citric acid and citric acid salt. The same objection was noted by the Examiner regarding the term "aggregate," in claims 13 and 15, and for the same reason. As noted in the most recent interview, however, the data in Table 1 relates to formulations that necessarily include a mixture of citric acid and citric acid salt. In Stern-II, paragraphs 5-6, Dr. Stern explains that, in both Tables 1 and 3, citric acid at concentrations of 10 mM or higher necessarily exists as a mixture of citric acid and citric acid salt when buffered to pH 3.7 or higher as both Tables 1 and 3 require. Table 1 thus supports claim language to a mixture. Moreover, the original specification teaches that (1) citric acid, (2) citric acid salt or (3) a combination of the two, may all be used throughout the broader concentration range of 10-50 mM. See Column 1, lines 50-55 of the applicant's original patent

6,440,392. By teaching the interchangeability of these agents throughout the 10-50 mM range, applicant necessarily taught their interchangeability within the narrower 10-25 mM range. Thus, all claim recitations of 10-25 mM are properly supported by the original specification, at Table 1 and elsewhere.

For all of the foregoing reasons, it is urged that the claims are supported by the specification as originally filed, and that the rejection under 35 U.S.C. § 112 should be withdrawn. It is believed that an agreement was reached at the recent interview that the new matter rejection would be withdrawn once Dr. Stern submitted a declaration (as he has now done) establishing that Table 1 involves a mixture of citric acid and citric acid salt.

ANTICIPATION REJECTION OVER GREBOW (U.S. PATENT 5,026,825)

In the most recent Office Action, claims 13-14, 17, 20-23, 34, 40-42 had been rejected by the Examiner under 35 U.S.C. § 102(b) as allegedly anticipated by Grebow et al., U.S. Patent 5,026,825. Among the limitations of the rejected claims that are not disclosed by Grebow is that citric acid (and/or citric acid salt) be present at a concentration between 10 and 25 mM (claims 13, 14, 17, 20, 21, 34, 40, 41 and 42) or between 10 and 50 mM (claims 22 and 23). The Examiner had alleged that applicant's narrow 10-25 or 10-50mM concentration range is anticipated by Grebow's discussion of using a 10 to 500 mM concentration of buffering agents, one of which may be citric acid and potassium or sodium citrate (see Grebow, column 11, lines 35-47). This very broad range set forth in Grebow (10-500mM) is not sufficient to anticipate the much narrower range recited in applicant's claims (10-25 mM or 10-50 mM). While such overlapping ranges between the prior art and later patent claims present a number of complex considerations under the law of obviousness as discussed in the obviousness section *infra* , it is not an anticipation. See *Atofina v. Great Lakes Chemical Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) where the court held that a prior art temperature range of 100 to 500°C does not anticipate patent claims reciting a temperature range of 330 to 450°C. The range claimed by applicant herein is even narrower, relative to the prior art range, than the range the *Atofina* court held not to be anticipated. Thus, Grebow does not anticipate applicant's claims as a matter of law. It is believed that agreement was

reached at the recent interview that the anticipation rejection over Grebow would be withdrawn. Such action is solicited.

ANTICIPATION REJECTION OVER CHIODINI (U.S. PATENT 5,719,122)

Claims 13-14, 17-18, 20-23, 34, 38, 40-42 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Chiodini et al. Among the limitations of the rejected claims that are not disclosed by Chiodini is that citric acid (or citric acid salt or a mixture) be present at a concentration between 10 and 25 mM (claims 13, 14, 17, 20-21, 34, 38, 40-42) or between 10 and 50 mM (claims 22 and 23) or 10 mM (claim 18). Chiodini fails to anticipate for the same reason as does Grebow. Namely, Chiodini's broad discussion of using citrate buffer (See Chiodini, Column 6, lines 13-25) does not anticipate a specific recitation of a very narrow range of citrate. See, *Atofina v. Great Lakes Chemical Corp., supra.*

The Examiner cites Example 19 of Chiodini as a specific anticipation. However, it is axiomatic that anticipation requires that each and every element of the claim be present in the cited reference. Scripps Clinic & Research Foundation v. Genentech, Inc, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991). There must be no difference between the claimed invention and the reference disclosure. Ibid. Example 19 of Chiodini specifically requires that pH be adjusted to 6 (See Chiodini, Col 11, lime 57), which is well out of the pH range of applicant's claims 13, 14, 17, 20-21 34, 38 40-42. It is believed that agreement was reached at the recent interview that the anticipation rejection over Chiodini would be withdrawn with respect to these pH-limited claims. In addition, three other claims are distinguishable from Chiodini in view of specific limitations therein. Claim 18 recites a specific combination of specific concentrations of ingredients, which combination is not believed to be set forth in Chiodini. Likewise, claims 22 and 23 are method claims wherein citric acid (and/or citric acid salt) are utilized within claimed concentration ranges for the purpose of enhancing bioavailability or shelf stability. Instead, Chiodini discusses using citric acid and sodium citrate as buffering agents to regulate pH. At page 4 of her Office Action, the Examiner herself notes this pH-related purpose of citrate buffering systems in Chiodini. For all of the foregoing reasons, it is urged that the anticipation rejection over Chiodini should be withdrawn.

OBVIOUSNESS REJECTION OVER GREBOW IN VIEW OF AZRIA (U.S. Patent 5,733,569)

Claims 15-16, 18-19, 24-33, 35-39 and 43-44 stand rejected by the Examiner under 35 U.S.C. § 103 as allegedly obvious over Grebow (cited above) in view of Azria (U.S. Patent 5,733,569). In summary of the arguments that follow, applicant believes that, (1) under legal precedents discussed below, Grebow's recitation of a broad range of 10 to 500 mM citrate (especially in view of Grebow's preference for 50-200 mM) is not sufficient to render obvious the much narrower recitation set forth in applicant's claims (10-50 mM in some claims 10-25 mM in other claims, and even narrower concentrations in other claims); and (2) The secondary reference, Azria, adds nothing to the deficiencies of Grebow regarding citrate because Azria does not use citrate at all.

The Court of Appeals has set forth a two-step analysis for determining obviousness where there is a partial overlap between a prior art mathematical range and a later-claimed mathematical range. In the first step, the burden is upon the Examiner to establish a *prima facie* case of obviousness by showing (A) that there is overlap between the claimed range and prior art range, and (B) that the range recited in the prior art was utilized for the same purpose as the range recited in the patent applicant's later claim. *In re Fine*, 837 F.2d 1071, 1075-76 (Fed. Cir. 1988). If the Examiner cannot make a *prima facie* case, applicant's patent claim is allowable without the second step of the analysis even arising.

On the other hand, when the Examiner does make a *prima facie* case of obviousness, a second analysis step arises wherein applicant's patent claim becomes allowable if applicant rebuts the *prima facie* case with a showing of nonobviousness, such as a showing that unexpected advantages are achieved within applicant's claimed range that are not achieved elsewhere within the prior art range *In re Peterson*, 315 F.3d 1325 (Fed. Cir. 2003); *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995).

The Court of Appeals has long recognized that the mere overlap of numerical ranges between the prior art and the range cited in a later patent claim need not render obvious the patent claim. For example, the court held in *In re Soni,* 54 F.3d 746, 751 (Fed. Cir. 1995) that prior art using polymers of a wide variety of molecular weights did not render obvious a later patent claim specifically reciting polymers of a molecular weight "greater that 150,000." Likewise, the court

held in *In re Fine,* 837 F.2d 1071, 1075-76 (Fed. Cir. 1988) that a prior art temperature range of 675-725 C did not render obvious a later patent claim reciting a temperature range of 600-1700 C where, as here, the overlapping ranges were for different purposes. The concept was recently explained by the Court in *Iron Grip Barbell, Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1321 (Fed. Cir. 2004), as follows:

> "Thus, simply because an invention falls within a range disclosed by the prior art does not necessarily make it *per se* obvious. Both the genus and species may be patentable."

In *Fine, supra*, the claims at issue were deemed allowable because the Examiner had failed to make a *prima facie* case of obviousness. In *Soni, supra*, the claims were deemed allowable even though applicant admitted that the Examiner had made a *prima facie* case, because applicant then successfully rebutted that case by showing unexpected advantages within the mathematical range of applicant's claims. In the present application, as discussed in separate sections, *infra*, neither prong of the two-step analysis supports a finding of obviousness. First, applicant urges that *prima facie* obviousness is not established by Grebow's 10-500mM range for its buffer because applicant uses citrate for the entirely different purposes of providing good bioavailability and shelf stability - - not for providing pH stability as disclosed by Grebow. Second, even if the Examiner had made a *prima facie* case, applicant has rebutted that case with a clear showing that entirely unexpected advantages are achieved within applicant's narrow range of citrate concentration, relative to the much broader range recited by Grebow. Each of these issues is discussed in greater detail below.

PRIMA FACIE OBVIOUSNESS IS NOT ESTABLISHED BY GREBOW IN VIEW OF AZRIA

For convenience, applicant reproduces below the paragraph from the Grebow reference on which the Examiner places significant reliance in alleging that Grebow suggests the narrow range of citric acid (and/or citric acid salt) concentration recited in applicant's claims:

> "Preferably, the subject calcitonin is formulated in water or a pharmaceutically acceptable aerosol composition. Nasal spray solutions are especially preferred with water or in buffer at a ph [sic] of between about 3.0 to 8.0, using a pharmaceutically acceptable

> buffer system. The buffer system of the present invention preferably contain a sodium or potassium phosphate/phosphoric acid buffer or a sodium or potassium acetate/acetic acid buffer or a sodium or potassium citrate/citric acid buffer in the range of 0.01 M to 0.5 M and preferably in the range of 0.05M to 0.2M. This concentration was found effective to provide stability of the dissolved calcitonin in the diluent base or vehicle." (Emphasis added)."

All rejected claims require citric acid (and/or citric acid salt) in a concentration range no broader than 10-50 mM, and in many claims 10-25mM or an even narrower concentration range. Applicant uses citric acid (and/or citric acid salt) to simultaneously enhance bioavailability and shelf stability, a result achieved only within applicant's narrow concentration range. See Tables 1 and 3 of applicant's original U.S. Patent 6,440,392. Table 1 establishes minimum citrate levels for good bioavailability, and Table 3 shows unexpected loss of shelf stabilty if citrate concentration is too high. By contrast, Azria does not use citric acid at all. And in many embodiments, neither does Grebow. In those few embodiments where Grebow uses citric acid and/or citric acid salt, it is solely as a buffer to stabilize pH, as evidenced (1) by Grebow's numerous examples that utilize different buffering agents in lieu of citric acid, and (2) by Grebow's enormous concentration range of 10-500 mM recommended for the variety of different Grebow buffer systems at Col. 11, lines 35-47 of Grebow.

The Examiner emphasizes Grebow's statement, at Col 11, lines 45-47, that "[t]his concentration was found effective to provide stability of the dissolved calcitonin in the diluent base or vehicle" as allegedly relating to shelf stability, one of applicant's purposes. In context, however, it is urged that Grebow is not referencing such shelf stability. The Grebow reference does not test for shelf stability. The only reported tests are on bioavailability effects provided by aminolevulinic acid in formulations totally devoid of citric acid or citric acid salt. The Grebow bioavailabilty tests tested the value of aminolevulinic acid in formulations buffered with acetate -- not citrate. See Grebow Col. 14, lines 29-40. Because Grebow's reference to "stability" is the concluding sentence of a paragraph generically describing a wide variety of buffer systems (including many that are not based on citric acid or citric acid salt at all), this statement clearly appears to refer to pH stability or to initial solubility of calcitonin in the solution -- not to any inherent properties citric acid (and/or citric acid salt) may have for balancing bioavailability and shelf stability as

taught be applicant. Dr. Stern so interprets Grebow's statement about stability at Stern-II, paragraphs 7-10.

Thus, Grebow often does not use citric acid (and/or citric acid salt) at all. When used, it is only in buffer systems for the purpose of adjusting pH, whereas applicant uses citric acid (and/or citric acid salt) very differently -- for a combination of bioavailability and shelf stability enhancement. Where, as here, the prior art discusses a broad citric acid concentration range of 10-500 mM that only slightly overlaps the range of 10-25 recited in applicant's claims (10-50 mM in some claims), a *prima facie* case of obviousness cannot arise unless the prior art uses that range of citric acid (and/or citric acid salt) for the same purpose for which it is used by applicant. *In re Fine*, 837 F.2d 1071, 1075-76 (Fed. Cir. 1988). The legal result that flows from Grebow's different purpose for its range relative to applicant's range was explained as follows by the Court of Appeals in *Fine*:

> "A material limitation of the claimed system is that the conversion to nitric oxide occur in the range of 600°C to 1700°C."
>
> ***
>
> "Although Eads describes a preferred temperature of 675°C to 725°C, the purpose of this range is different from that of Fine."
>
> ***
>
> "There is partial overlap, of course, but this is mere happenstance. Because the purposes of the two temperature ranges are entirely unrelated, Eads does not teach use of the claimed range. See, *In re Geiger*, 815 F.2d at 688, 2 USPQ2d at 1278. The Board erred by concluding otherwise."
>
> ***
>
> "[W]e reverse for failure to establish a *prima facie* case of obviousness . . ."

Fine at 1075-76.

Although *Fine* is an old case, it is still good law. Some newer cases state, without discussion, that a range overlapping with the ranges in prior art establishes a presumptive or *prima*

facie case of obviousness. *See, e.g., Ornco Corp. v. Align Technology, Inc.,* 463 F.3d 1299, 1311 (Fed. Cir. 2006); *In re Harris*, 409 F.3d 1339, 1341 (Fed. Cir. 2005), *cert. denied sub nom.* Harris v. Dudas, 546 U.S. 1090 (2006) ; *Iron Grip Barbell Co. v. York Barbell Co.,* 392 F.3d 1317, 1322 (Fed. Cir. 2004); *In re Peterson,* 315 F.3d 1325, 1329 (Fed. Cir. 2004). None of these cases, however, deal with the situation raised in *Fine*, where the prior art uses the range in question for a ***different purpose*** than that claimed by applicant.

Moreover, these cases rely on a trio of cases where *prima facie* obviousness was not in dispute, or where the court specifically noted that no different purpose was claimed. *See In re Geisler,* 116 F.3d 1465, 1469 (Fed. Cir. 1997) ("[applicant] concedes that the Examiner was correct to find the claims *prima facie* obvious"; decision turned on whether that presumption had been rebutted); *In re Woodruff*, 919 F.2d 1575, 1577 (Fed. Cir. 1990) (court specifically noted that "we do not agree that [applicant] has allegedly discovered and claimed what can be termed a new ***purpose*** for performing the claimed method") (emphasis in original); *In re Malagari*, 499 F.2d 1297, 1303 (Fed. Cir. 1974) (discussion focuses on rebuttal of *prima facie* case of obviousness only).

None of these cases determine that a *prima facie* case of obviousness exists where, as in *Fine* and in the instant case, the range recited in the prior art relates to a ***different purpose*** than that claimed by the applicant, nor has research revealed a case where the Federal Circuit has so held.

In short, notwithstanding language about overlapping ranges establishing a presumption of obviousness, that presumption does not obtain unless the prior art and the applicant seek to use the overlapping range for the same purpose. *Fine,* 837 F.2d at 1075-76.

For all of the foregoing reasons, it is urged that *prima facie* obviousness has not been established.

EVEN IF *PRIMA FACIE* OBVIOUSNESS HAD BEEN ESTABLISHED,
APPLICANT EFFECTIVELY REBUTTED THAT FINDING BY
SHOWING UNEXPECTED RESULTS RELATIVE TO GREBOW/AZRIA

Even if a *prima facie* case of obviousness had been established based on overlapping citric acid ranges between the prior art and applicant's claims (and no such prima *facie case* is believed

to have been established for reasons given in the prior section), applicant has overcome the assertion of obviousness with extensive evidence of unexpected results. As explained by the court of Appeals in *In re Peterson*, 315 F.3d 1325 (Fed. Cir. 2003):

> "In general, an applicant may overcome a *prima facie* case of obviousness by establishing 'that the [claimed] range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range.' *In re Geisler*, 116 F.3d at 1469-70, 43 USPQ2d at 1365 (alteration in original) (quoting *In re Woodruff*, 919 F.2d at 1578, 16 USPQ2d at 1936)."

The narrow range of citric acid (and/or citric acid salt) recited in applicant's claims unexpectedly avoids a significant drop in shelf stability at the higher concentrations the cited Grebow reference would permit, Grebow apparently being entirely unaware of the relationship applicant discovered between shelf stability and citric acid (and/or citric acid salt) concentration. Grebow permits an extremely broad range of buffer concentration from 10-500 mM (stated as 0.01M to 0.5M at column 11, line 44), and states a preference for the range of 50 mM to 200 mM at column 11, line 45 (stated as 0.05 M to 0.2M). This stated preference teaches away from Applicant's lower claimed range in a manner that could significantly harm Grebow's shelf stability. Table 3 of Applicant's application clearly shows a significant drop in shelf stability at concentrations of citric acid (and/or citric acid salt) above 50 mM, and extremely poor shelf stability at 100 mM. See Table 3, row 5 at column 6, line 32 of Applicant's '392 Patent. New corrected Table 3 submitted herewith shows a less draconian drop than had prior uncorrected Table 3, yet continues to show significant shelf-stability loss at higher citrate concentrations. Yet, Grebow, in direct contradiction to Applicant's teachings, suggests a preference at column 11, lines 44-45 of using a high buffer concentration range that extends well beyond any concentration deemed appropriate by Applicant's data.

In the attached Stern-II Declaration, Dr. Stern states that Applicant's observed enhancement to shelf stability obtained in the narrow, and low, concentration of citric acid (and/or citric acid salt) recited by the present claims is unexpected (Stern-II, paragraphs 11-13). He hypothesizes, based on evidence discussed in more detail at Stern-II, paragraph 12, that the unexpected drop in shelf stability that is shown as citrate concentration increases in Table 3, is at least partially the

result of formation of an adduct between citric acid and the calcitonin active agent. Dr. Stern does not believe that the cited prior art expected either of (1) the extensive drop-off of shelf stability at higher concentrations of citric acid (and/or citric acid salt) or (2) the apparent formation of the adduct. See Stern-II , paragraph 11. Dr. Stern's conclusion is corroborated by the Grebow prior art cited by the Examiner. Grebow could not have expected adduct formation or extensive loss of shelf stability at high citrate concentrations because Grebow specifically recommends higher concentrations from 50-200 mM (at Column 11, lines 44-45) as a "preference."

In *In re Soni*, 54 F.3d 746 (Fed. Cir. 1995), the court of Appeals set forth the standard of evidence needed to establish unexpected results and thus to overcome any *prima facie* case of obviousness that may have been made. The majority opinion in *Soni* held that an applicant's mere statement that improved results within the claimed range were "unexpected" would suffice in the absence of evidence to the contrary. *Soni* at 751. A dissenting opinion stated that the majority should have required evidence in support of the conclusion that improved results were unexpected. Here, Dr. Stern has met both standards and his conclusion is supported by the Examiner's cited Grebow prior art itself. Dr. Stern has (1) stated that it was unexpected that the low claimed concentrations would provide improved results (Stern-II, paragraphs 11 and 13); (2) explained why it was unexpected with reference to significant data and evidence of an unexpected mechanism (Stern-II, paragraphs 12-13); and (3) pointed to prior art statements which the cited Grebow reference would not have made if applicant's concentration findings had been expected (Stern-II, paragraph 13 and Grebow Column 11, lines 44-45). As noted previously, the secondary reference, Azria , does not utilize citrate, and therefore cannot overcome any of Grebow's deficiencies as regards citrate. For all of the foregoing reasons, it is urged that the obviousness rejection over the combination of Grebow and Azria should be withdrawn.

In accordance with the duty of disclosure, Dr. Stern presents (at Stern-II, paragraph 20, and referenced exhibits thereto) other data regarding shelf stability, beyond the data already reported in Table 3 of applicant's specification. Corrections to the specification are also noted in Stern-II, *e.g.*, paragraphs 15-21.

Finally, applicant wishes to clarify arguments made at page 9 of the Amendment mailed March 21, 2006 regarding prior art use of citric acid as it relates to certain method claims. It is the

"prior art" cited by the Examiner in the immediately preceding Office Action that is being distinguished there. Other prior art cited in applicant's Information Disclosure Statement filed May 5, 2004, *e.g.*, U.S. Patent No. 5,912,014 (on which Dr. Stern is a co-inventor), utilized acid -- any acid, including citric -- in an oral calcitonin formulation for the purpose of reducing pH in the intestines. This in turn reduced calcitonin degradation by intestinal proteases that are more active at higher pH levels. This reduction in calcitonin degradation, of course, improved oral bioavailability. In contrast, claims 22 and 23 of the present application (discussed at page 9 of the March 21 , 2006 Amendment) utilizes citric acid and/or citric acid salt -- within carefully defined concentration ranges and in a pH-independent manner -- to provide good nasal bioavailability (*e.g.*, claim 23 and claims dependent therefrom) and good shelf stability (*e.g.*, claim 22 and claims dependent therefrom). Nothing in applicant's prior submissions herein, including page 9 of the March 21, 2006 Amendment, was intended to imply that citric acid has not been utilized in the prior art in the manner set forth in prior art U.S. Patent No. 5,912,014.

It is believed that the application is now in condition for allowance. Issuance of a notice of allowance is solicited.

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Mail Stop Reissue, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on September 7, 2007:

William O. Gray, III
Name of applicant, assignee or Registered Representative

Signature

September 7, 2007
Date of Signature

Respectfully submitted,

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WOG:db

APPENDIX A

Claim Number (Status)	Nature of Change/Recitation	Supporting Text in Original Patent
1-12 (canceled)	n/a	n/a
13 (pending)	citric acid concentration; rewritten in independent form; "and/or" changed to Markush format	Table 1; Table 3
14 (pending)	claim dependency only	original claim 14
15 (pending)	citric acid concentration; rewritten into independent format; "and/or" changed to Markush format	original claim 15; Table 1; Table 3
16 (pending)	claim dependency only	original claim 16
17 (pending)	claim dependency only	original claim 17
18 (pending)	no change	original claim 18
19 (pending)	typographical error "MRC"; no substantive change	original claim 19
20 (pending)	claim dependency only	original claim 20
21 (pending)	no change	original claim 21
22 (pending)	"about" removed	original claim 22
23 (pending)	"about" removed	original claim 23
24 (pending)	citric acid concentration	Claim 19
25 (pending)	pH range	col. 3, line 12
26 (pending)	pH range	col. 3, line 12
27 (pending)	aqueous saline	col. 3, line 2
28 (pending)	viscosity	col. 3, lines 19-20
29 (pending)	polyoxyethylene (20) sorbitan monooleate	original claim 16
30 (pending)	preservatives	original claim 17

Claim Number (Status)	Nature of Change/Recitation	Supporting Text in Original Patent
31 (pending)	aqueous saline; osmotic pressure	col. 3, line 2; col. 3, lines 16-18
32 (pending)	salmon calcitonin	examples 1, 2 and 3
33 (pending)	salmon calcitonin	examples 1, 2 and 3
34 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
35 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
36 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
37 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
38 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
39 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
40 (pending)	method of nasal administration	original claim 20; col. 3, lines 43-56
41 (pending)	pH range; citric acid concentration	col. 3, line 12; Tables 1 and 3
42 (pending)	pH range; citric acid concentration	col. 3, line 12; Tables 1 and 3
43 (pending)	aqueous saline; osmotic pressure	col. 3, line 2; col. 3, lines 16-18
44 (pending)	aqueous saline; osmotic pressure	col. 3, line 2; col. 3, lines 16-18